REMARKS

Reconsideration of the application in light of the following remarks is respectfully requested.

I. Status of the Claims. Claim 46 is canceled by this amendment. Therefore, claims 37, 42-44, 48, 52-54, 56 and 57 are presently at issue in the application.

a. *Claim amendments*: Claims 37, 48 and 57 have been amended.

Claim 37 has been amended to recite a method of suppressing an ongoing autoimmune disease by the administration of a bystander antigen. Support for the amendment is found in the specification at page 11, lines 1-12 and page 12, lines 26-32. No new matter has been introduced by the amendment.

Claims 48 and 57 have been amended to recite a pharmaceutical dosage form for suppressing an autoimmune disease and Type I diabetes, respectively. Support for the amendment is found in the specification at page 11, lines 1-12 and page 12, lines 26-32. No new matter has been introduced by the amendment.

Claim 46 has been canceled without prejudice or disclaimer.

II. Claim Rejections. Presently, claims 37, 42-44, 46, 48, 52-54, 56 and 57 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Particularly, the Examiner maintains the following rejections, each of which will be discussed in turn:

(1) The present claims, drawn to methods of treating an autoimmune disease necessarily include prevention of an autoimmune disease and therefore are not enabled as applicants have not demonstrated that any level of suppression is sufficient to prevent an autoimmune disease; and

(2) given the unpredictability in the art at the time the application was filed and the limited teachings of the specification, the presently claimed invention, which requires administration of a bystander antigen and the induction of tolerance in a host, is not enabled.

A. Claims directed to abatement of an autoimmune response by oral administration of a bystander antigen are enabled.

The Examiner has rejected claims 37, 42-44, 46, 48, 52-54, 56 and 57 under §112, first paragraph, for lack of enablement. The Examiner contends that the present specification does not enable claims directed to the treatment of an autoimmune disease by administration of a bystander antigen. Particularly, the Examiner maintains that the present claims necessarily include prevention of an autoimmune disease and that applicants have not demonstrated any level of suppression which is capable of preventing an autoimmune disease.

In response, and without conceding the correctness of the Examiner's rejection, claim 46 has been canceled and claims 37, 48 and 57 have been amended. Claims 37 and 48 have been amended to recite a method and pharmaceutical dosage form for suppressing an ongoing cell mediated autoimmune disease by the administration of a bystander antigen. Claim 57 has been amended to recite a pharmaceutical dosage form for the suppression of Type I diabetes. Support for the present amendments is found in the specification at page 11, lines 1-12 and page 12, lines 26-32. The amendments do not add new matter to the specification.

The present amendments were made upon the recommendation of the Examiner in order to place the claims in better condition for allowance (*See e.g.* Paper No. 27, page 3). Applicants submit that the present amendments render the Examiner's present rejection of claims 37, 42-44, 48, 52-54, 56 and 57 for lack of enablement, moot. Accordingly, the rejection should be withdrawn.

B. The teachings of the specification enable one of ordinary skill in the art to induce oral tolerance to bystander antigens and practice the full scope of the presently claimed invention.

The Examiner contends that the present claims are not enabled because at the time the application was filed, one of ordinary skill could not predictably induce a tolerizing response by administering a bystander antigen and therefore could not practice the claimed invention.

Applicants respectfully traverse the present rejection and submit that the Examiner has mischaracterized the state of the art at the time the application was filed. Thus, contrary to the

contention of the Examiner, the art was not so unpredictable as to prevent one of ordinary skill from practicing the full scope of the claimed invention.

The Examiner has cited Tisch et al., *Proc. Natl. Aacd. Sci.* (1994) 91:437-438, (of record, herein referred to as "Tisch") as being representative of the skill in the art at the time the application was filed. The Examiner specifically cites Tisch, stating, "It is naïve to expect that one form of antigen-specific will be effective for the *treatment of all* T-cell mediated autoimmune diseases." *See* Office Action, page 4 (emphasis added). The Examiner also cites Tisch for the position that inducing CD8+ regulatory T-cells is variable and dose dependent. *See* Office Action, page 4. Thus the Examiner maintains, provided the teachings of Tisch, the art was highly unpredictable and therefore the present claims are not enabled.

Applicants respectfully submit that the Examiner's characterization of the teachings of Tisch are misplaced for two reasons: (1) the teachings of Tisch, relied upon by the Examiner, are directed to treatment of T-cell mediated autoimmune diseases, and (2) Tisch cites to several successful studies that have successfully induced oral tolerance by the administration of an antigen.

First, the teachings of Tisch, relied upon by the Examiner, are directed to treatment of T-cell mediated autoimmune diseases, while the presently amended claims are directed to suppression of ongoing T-cell mediated autoimmune diseases. As discussed above, the present amendments have been made at the request of the Examiner.

Second, the Examiner has mischaracterized the teachings of Tisch by citing exclusively to teachings directed to treatment of autoimmune diseases. Contrary to the characterization of the Examiner, Tisch as a whole teaches that inducing oral tolerization by administration of an antigen was predictable. Tish refers to the several investigations in which orally administered autoantigens resulted in tolerization of autoreactive T-cells. *See* Tish, page 437.

Additionally, Tisch refers to several studies that have demonstrated the use of a variety of bystander antigens to delay or suppress a variety of autoimmune diseases in various animal models, *e.g.*, IDDM, EAE, experimental autoimmune uveoretenitis, and adjuvant arthritis. *See* Tisch, page 438. Tisch also cites a successful human clinical trial in which administration of

type II collagen to patients suffering from severe active RA resulted in either abatement of symptoms associated with the disease or complete remission of the disease. *See* Tisch, page 438. Summarizing the successes of various investigators, Tisch states:

> It is possible via this approach [antigen driven bystander suppression] to treat an organ-specific autoimmune disease, despite the fact that the "initiating" autoantigen is not known. The clinical reports suggest that oral administration may allow for effective treatment of an ongoing autoimmune response.

Tisch, page 438. Given the fact that Tisch cites several successful laboratory studies and an effective human trials, Tisch is not in fact supportive of the Examiner's position.

Should the Examiner maintain the position that the art was so unpredictable, despite the present remarks, applicants maintain that the present claims are enabled by the specification. The enablement requirement of §112 does not require that the applicant describe how to make and use all of the claimed embodiments, even when the art is unpredictable. In fact the Federal Circuit has stated:

> ...we do *not* imply that patent applications in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art.

In re Vaeck, 947 F.2d. 488 (Fed. Cir. 1991) *citing In re Angstadt*, 537 F.2d 498 (CCPA 1976) (emphasis in original). Rather, the disclosure must provide the skilled artisan with sufficient guidance to determine, without undue experimentation, which claimed embodiments posses the claimed utility. *Id.* To determine whether or not practice of the claimed invention requires undue experimentation, several factors must be considered: (1) the predictability or unpredictability of the art, (2) the state of the prior art (3) the relative skill of those in the art, (4) breadth of the claims, (5) the amount of direction provided, (6) the nature of the invention, (7) the presence or absence of working examples, and (8) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

Applicants submit that it would not have required undue experimentation to determine which bystander antigens possessed the claimed utility and to practice the full scope of the presently claimed invention. Applicants position is premised on the fact that: (1) the art was predictable, (2) the claims are narrowly drawn, (3) the specification provides detailed guidance and working examples, (4) the level of skill in the art was high, and (5) only a moderate amount of routine experimentation would be required.

As discussed above, inducing oral tolerance by the administration of an antigen was predictable at the time the application was filed. The level of predictability is evidenced by numerous reports of inducing oral tolerization and the subsequent suppression of various autoimmune diseases. *See* Tisch, page 437-438. The teachings of Tisch are buttressed by the lengthy history of inducing oral tolerization. Oral tolerance was reported as early as 1911, and its use to suppress autoimmune processes has been the subject of investigation since 1988. *See* Miller et al. *Proc. Natl. Aacd. Sci.* (1992) 89:421-425 (of record). Therefore, applicants submit that one of ordinary skill could predictably induce antigen specific CD8+ T-cells by administering a bystander antigen, and thereby practice the claimed invention of suppressing an ongoing autoimmune response.

Not only was the state of the art predictable at the time the application was filed, but the present claims do seek to claim an entirely new genus and the specification provides a detailed description of how to practice the claimed invention. Additionally, the level of skill in the art at the time the application was filed was such that only a moderate amount of routine experimentation would have been necessary for one of ordinary skill to identify all of the bystander antigens which possess the claimed utility.

The claims of the present application are drawn to a method of suppressing an ongoing autoimmune response by the administration of a bystander antigen. Thus, applicants do not seek to broadly claim an entire genus, *e.g.*, all antigens, but rather only those specific bystander antigens capable of suppressing an autoimmune response. Applicants have identified a number of exemplary and non-limiting bystander antigens and the corresponding autoimmune diseases, which they believe to be within the scope of the present invention. *See, e.g.*, Table 1, page 19.

Applicants have also described in great detail experiments that may be carried out to determine the ability of each of the bystander antigens to induce tolerance and suppress an autoimmune response. *See* Specification, Example 1, page 34, lines 1-12. Therefore, determination of bystander antigens embraced by the present claims and having the claimed utility would only require routine experimentation and would be well within the ability of one of ordinary skill in the art.

As evidence of the amount of experimentation required and the ability of one of ordinary skill to practice the presently claimed invention, applicants refer the Examiner to the declaration of Dr. Von Harreth (of record).[1] In his declaration, Dr. Von Harreth stated that in his opinion the specification provided detailed guidance and teachings such that the skilled artisan would be able to readily identify and assay bystander antigens contemplated by the present invention. *See* Von Harreth, page 9, para. 14, and page 10, para. 15. Such selection and experimentation, Dr. Von Harreth stated, would be routine and would employ techniques widely known and practiced at the time this application was filed. Von Harreth, page 10, para. 14. Therefore, one of ordinary skill in the art would be capable of practicing the presently claimed without undue experimentation and as such that present claims are enabled by the specification.

Provided that the teachings of Tisch suggest that one of ordinary skill could predictably induce oral tolerization by administration of a bystander antigen and that selection of bystander antigens having the claimed utility would not require undue experimentation, as supported by the declaration of Von Harreth, the applicants submit that the present claims are enabled by the specification. Therefore the rejection of claims 37, 42-44, 48, 52-54, 56 and 57 for lack of enablement should be withdrawn.

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[1] Von Harreth Declaration ("Von Harreth"), submitted November 1, 2000, with Supplemental Response, Paper No. 25. Dr. Von Harreth is the author of over 30 publications on the subject of immunology of the autoimmune diseases, including several articles relating to bystander suppression.

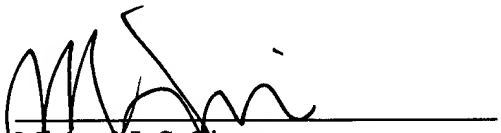
CONCLUSION

Each and every point raised in the Office Action dated December 18, 2002 has been addressed on the basis of the above remarks. In view of the foregoing it is believed that the presently pending claims are in condition for allowance, and it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted

Dated: March 1, 2004



Michael J. Sullivan
Reg. No. 54,479
Agent for Applicants

DARBY & DARBY
Post Office Box 5257
New York, NY 10150-5257
Phone (212) 527-7700